REMARKS

Reconsideration and withdrawal of the rejections of this application is respectfully requested in view of the remarks and amendments herein.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1-4, 6-7, 9-15 and 30-36 are currently pending. Claims 1-4, 6, 9-11, 14 and 15 have been amended, claims 5, 8, 16 and 21-29 have been cancelled, and new claims 30-36 have been added, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that both the original claims and the claims as presented herewith are patentably distinct from the references cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the amendments are made simply for clarification and to round out the scope of protection to which Applicant is entitled.

II. ARRANGEMENT OF THE SPECIFICATION

The Examiner is thanked for his suggestions regarding the arrangement of the specification. However, Applicants have decided to forgo any changes to the specification at this time.

III. OBJECTION TO THE CLAIMS

Claim 5 has been objected to under 37 C.F.R. §1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The objection is respectfully traversed. The cancellation of claim 5 renders the objection moot. Consequently, reconsideration and withdrawal of the objection is respectfully requested.

Additionally, the Office Action objected to claims 24 and 28 on the grounds that they are allegedly substantial duplicates of claims 22 and 26, respectively. The objection is respectfully traversed. Claims 22, 24, 26 and 28 have been cancelled, rendering the objection moot. Consequently, reconsideration and withdrawal of the objection is respectfully requested.

IV. THE REJECTIONS UNDER 35 USC §112, 1st PARAGRAPH, ARE OVERCOME

Claims 1-16, 21, 23, 25 and 27 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the application at the time of filing. The rejection is respectfully traversed.

The Office Action again alleges that the claims are directed to an anti-fouling composition comprising an enzyme obtained or obtainable from a marine organism, but that the specification provides only a single representative species: hexose oxidase from *Chondrus cripus*.

In the Response filed February 25, 2004, Applicants pointed to the specification on page 7, lines 3 to 8, for the teaching of a number of suitable enzymes other than hexose oxidase. The present Office Action states that the identification of other enzymes is not enough; that a specific structural feature of these additional enzymes is also required. It is respectfully sumitted that the specific structural feature requested by the Office Action is inherent in the previously presented list of enzymes. Each enzyme described was an **oxidase**. As defined in Biochemistry (Matthews, C.K. and Van Holde, K.E., The Benjamin/Cummings Publishing Co., Inc., 1990) on page 532 (copy attached), "[t]he term oxidase is applied to enzymes that catalyze the oxidation of a substrate by O_2 without incorporation of oxygen into the product." Accordingly, each of the enzymes identified in the specification on page 7, lines 3 to 8, catalyzes reactions using O_2 as a substrate, and the ability of the enzymes to catalyze such a reaction necessitates a structural relationship or similarity between the various enzymes.

The textbook Biochemistry, from which the definition of oxidase above was provided, was published in 1990 – earlier than the filing date of the present application. If one of skill in the art was aware in 1990 that oxidases possess similar characteristics and catalyze the same type of reactions, one of skill in the art at the time the present application was filed would certainly be aware that it would be possible to utilize other oxidases in place of one another.

Furthermore, one of skill in the art at the time the present application was filed would clearly also know how to obtain such oxidases, such that *Chondrus cripus* was not the only possible source for such oxidases. For example, the page of Biochemistry discussed above also states that as of 1990, there were over 200 known enzymes that use O_2 as the substrate, a large number of which can be considered oxidases. If such a large number of enzymes were known in

1990, it follows that their sources were also known, and that such enzymes would be readily obtainable by one of skill in the art.

Accordingly, it is clear that Applicants had possession of the present application at the time of filing, and reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1 to 16, 21, 23, 25 and 27 have also been rejected under 35 U.S.C. §112, first paragraph as the disclosure is allegedly enabling only for claims limited to an anti-fouling composition comprising *Chondrus crispus* hexose oxidase of SEQ ID No. 1 and any of its known substrates listed in the specification. The rejection is respectfully traversed.

The Office Action again states that one of skill in the art would not be able to make and use the present invention without additional guidance not present in the specification. Applicants respectfully disagree.

It is respectfully submitted that the assertion in the Office Action that undue experimentation is required to practice the instantly claimed invention is inaccurate. The Examiner is respectfully directed to *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), wherein the Federal Circuit stated at 1404 that:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing the factors summarized in *In re Wands*. These

factors include, for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims; all of which must be taken into account.

Applying the law to the instant facts, it is clear that enablement exists. As discussed above, the specification provides a number of other enzymes which may be used in the present invention, and one of skill in the art would not only be able to identify such enzymes, but would be able to obtain these from sources other than *Chondrus cripus*.

Again, Applicants respectfully submit that the Examples in the specification are intended to describe the invention by way of example *only* (page 20, line 31 to page 21, line 1) and are not intended to limit the scope of the invention. The description, when read as a whole, provides enough teaching to enable one of ordinary skill in the art to make and use the invention commensurate with the scope of the claims. In particular, the description provides one of ordinary skill in the art with teaching on how to generalize the Examples without undue experimentation.

Furthermore, Applicants respectfully remind the Examiner that a working example for each alternative combination of enzymes and substrates is not required in order for the application to be considered enabled. Based on the description in the specification as discussed above, one of skill in the art would have more than sufficient knowledge of oxidases and their reactions to substitute an enzyme or substrate into the Examples of the present application and obtain the required result.

Accordingly, it is respectfully submitted that the quantity of experimentation necessary is low; the amount of direction or guidance presented is high; the present application has adequate working examples of the invention; and the relative skill of those in the art is high.

Therefore, it is respectfully submitted that given the guidance provided by the specification and the well-developed skill of the artisan, the present application is fully enabled. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Furthermore, the Office Action rejected c1aims 1-16 and 21-29 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The rejection is respectfully traversed.

The rejection was based on the use of the terms "precursor enzyme", "obtained or obtainable" and "or a variant, homologue, derivative or fragment thereof." The claims as currently amended no longer contain any of these phrases, rendering the rejection moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Additionally, claims 5, 22, 24, 26, 28 and 29 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to define the metes and bounds of the claim. The rejection is respectfully traversed.

The Amendment herein has cancelled all of these claims, rendering the rejection moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

V. THE ART REJECTIONS ARE OVERCOME

Claims 1-16 and 21-29 were rejected under 35 U.S.C. §103 as allegedly unpatentable over European Patent 0 866 103 A1 (to Hamade *et al.*) in view of Hansen *et al.* (J. Biol. Chem. 272(17):11581-11587). Claims 1-16, 21, 23, 25 and 27 were also rejected under 35 U.S.C. §103 as allegedly unpatenatble over Hamade *et al.* (*supra*) in view of U.S. Patent 6,251,626 B1 (to Stougaard *et al.*). The rejections are respectfully traversed and will be addressed collectively.

Applicants respectively assert that Hamade *et al.* relates to a method for controlled release of compounds having antimicrobial activity and a coating composition capable of controlled release of compounds having antimicrobial activity. Specifically, the patent relates to a method for releasing a compound having antimicrobial activity from a matrix at a controlled rate, which comprises incorporating an enzyme and a substrate in the matrix beforehand to allow the enzyme and the substrate to react with each other in the matrix to thereby produce the compound having antimicrobial activity; and further relates to a coating composition comprising a film-forming resin, an enzyme, and a substrate, the enzyme said to be capable of reacting with the substrate to produce a compound having antimicrobial activity.

It is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780,

1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure**. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

The Office Action asserts that Hamade *et al.* teaches a method of preventing fouling of surfaces submerged in water by use of an anti-fouling anget that is produced by an enzyme acting on its substrate, and an anti-fouling composition which comprises the enzyme and its substrate. Specifically, the Examiner states that Hamade *et al.* describes "an enzyme substrate combination capable of producing hydrogen peroxide and [exemplifies] the enzyme-substrate combination with glucose oxidase-glucose and hexose oxidase-glucose" on page 5, lines 14-22.

Furthermore, the Examiner asserts that "the substrate of said oxidase can be produced within the composition by a second enzyme action on a precursor substrate such as the action of cellulase on cellulose to produce glucose" and cites Hamade *et al.*, page 5, lines 50-54 for such assertion.

During a series of telephonic interviews in August, beginning on or about August 3, 2004, the undersigned, and one of the inventors Dr. Charlotte Poulsen attempted to prove to the Examiner that the assertion that Hamade *et al.* teaches that "the substrate of said oxidase can be produced within the composition by a second enzyme action on a precursor substrate such as the action of cellulase on cellulose to produce glucose" is incorrect. It is again respectfully asserted that nowhere in Hamade *et al.* is the presence of culllulose mentioned. Rather, the portion of Hamade *et al.* cited by the Examiner actually states that:

> An enzyme-substrate combination capable of producing said decomposition product of chitosan is not particularly restricted. Preferred is the case in which the enzyme is a chitosan-decomposing enzyme and the substrate is chitosan.
>
> The chitosan-decomposing enzyme is not particularly restricted in kind but includes chitosanase, cellulase, lysothyme, and so forth.

Although cellulase is listed as a possible chitosan-decomposing enzyme, nowhere is the presence of cellulose mentioned. The Examiner has apparently interpreted this passage to mean that the phrase "[a]n enzyme-substrate combination capable of producing said decomposition product of chitosan is not particularly restricted" actually means that any enzyme and substrate may be used, regardless of whether the decomposition of chitosan is the result of the enzyme substrate interaction, and has accordingly substituted cellulose into the list of possible substrates due to the inclusion of cellulase as a possible enzyme.

During a second telephonic interview that occurred on or about August 12, 2004 between the Examiner, Thomas Kowalski and Angela Collison, the Examiner asserted that it was not possible for cellulase to act on chitosan and that if cellulase was present, cellulose was necessarily also present.

Again, Applicants assert that the Examiner is incorrect in this assumption. The Examiner's attention is respectfully directed to the accompanying Declaration by Dr. Charlotte Poulsen, wherein Dr. Poulsen discusses the section of Hamade *et al.* cited by the examiner phrase by phrase. As shown in the Declaration, the presence of cellulase does not require that cellulose be present. And, while Hamade *et al.* shows that the chitosan decomposing enzyme may change, the substrate must be chitosan in order for the enzyme activity to result in decomposed chitosan.

The Examiner's attention is also directed to the abstracts attached to the Declaration of Dr. Poulsen, which demonstrate that chitosan may be digested by cellulose. This confirms Applicants' previous assertions that the presence of cellulase in the list of possible enzymes found in Hamade *et al.* does not indicate the presence of cellulose; rather, cellulase is listed because it degrades chitosan.

Furthermore, neither Hamade *et al.*, Hansen *et al.* or Stougaard *et al.* provide any incentive or motivation to combine the teachings and arrive at the present invention. Additionally, one of skill in the art would have no expectation of success in doing so.

The Office Action admits that Hamade *et al.* does not teach the use of an enzyme from a maraine organism. As previously stated, Applicants have identified that the use of an enzyme obtained or obtainable from a marine organism provides numerous surprising advantages over the prior art. These advantages include those listed on pages 5 and 6 of the description, namely.

- long-term effectiveness in environments;

- high affinity for glucose;
- reduced enzyme requirements;
- improved activity at operational temperatures;
- utilization of safe and readily available substrates;
- improved salt tolerance; and
- resistance to degradation by fouling organisms.

These advantages make the anti-fouling composition of the present invention particularly suitable for use in the marine environment, such as on the hull of a marine vessel. This novel and inventive feature, wherein use is made of an enzyme obtained or obtainable from a marine organism, is not disclosed in Hamade *et al.*, nor is it disclosed in Hansen *et al.*, or Stougaard *et al.* Accordingly, the surprising results obtained by the present invention render the present invention non-obvious over Hamade *et al.*, alone or in any combination.

In summary, Hamade *et al.* provides no teaching that an enzyme obtained or obtainable from a marine organism would provide particular advantages in an anti-fouling composition. Hansen *et al.* and Stougaard *et al.* do not teach the use of hexose oxidase from *Chondrus crispus* in an anti-fouling composition, they simply teach that hexose oxidase from *Chondrus crispus* was known. Neither Hansen *et al.* nor Stougaard *et al.* would not provide the skilled person, who had Hamade *et al.* as a starting point, with any motivation to select, from the vast army of enzymes present in Hamade *et al.*, enzymes obtained or obtainable from a marine organism.

Accordingly, neither Hansen *et al.* nor Stougaard *et al.* remedy the deficiencies of Hamade *et al.* Therefore the rejections cannot stand; reconsideration and withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the amendment and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance, or an interview at a very early date with a view to placing the application in condition for allowance, are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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Cover

Dimer of *trp* repressor protein, with bound tryptophan (in blue). The protein binds to DNA and regulates expression of the *trp* genes that control tryptophan biosynthesis. Crystal structure by Paul Sigler et al.; image by Jane and David Richardson.

Frontispiece

Figure 11.15a The T state of aspartate transcarbamoylase, as determined by x-ray diffraction.

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Figures 2.2, 2.4, 2.7, 2.9, 2.10, 2.11, 2.13, 2.14, 3.5, 4.2, 4.11, 4.12b, 4.14, 4.15, 4.22, 5.12, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.11, 6.12, 6.13a–c, 6.14, 6.17, 6.19, 6.21, 6.23a, b, and d, 6.25c and d, 7.2, 7.3b, 7.6, 7.9, 7.12, 7.13, 7.14, 7.15, 7.16, 7.17, 7.18, 7.21, 7.23 (Hb molecule), 7.27, 7.28, 8.20, 8.21, 8.22, 8.23, 9.23, 15.7 copyright © Irving Geis.

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Credits for photographs appear on pages xi–xiii

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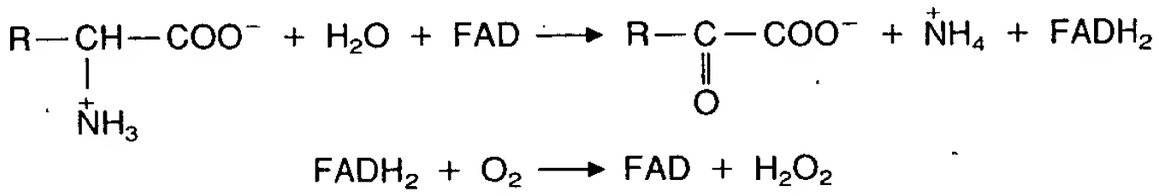
can calculate the efficiency for operation of this biochemical machine: (38 × 30.5)/2870, or 40%, under standard conditions. As noted earlier, the efficiency in vivo is probably higher.

Oxygen as a Substrate for Other Metabolic Reactions

In most cells at least 90% of the molecular oxygen consumed is utilized for oxidative phosphorylation. The remaining O_2 is used in a wide variety of specialized metabolic reactions. At least 200 known enzymes use O_2 as a substrate, and in this section we shall briefly categorize these enzymes. We also consider the metabolism of partially reduced forms of oxygen, which arise continually in all cells and are highly toxic because of their great reactivity.

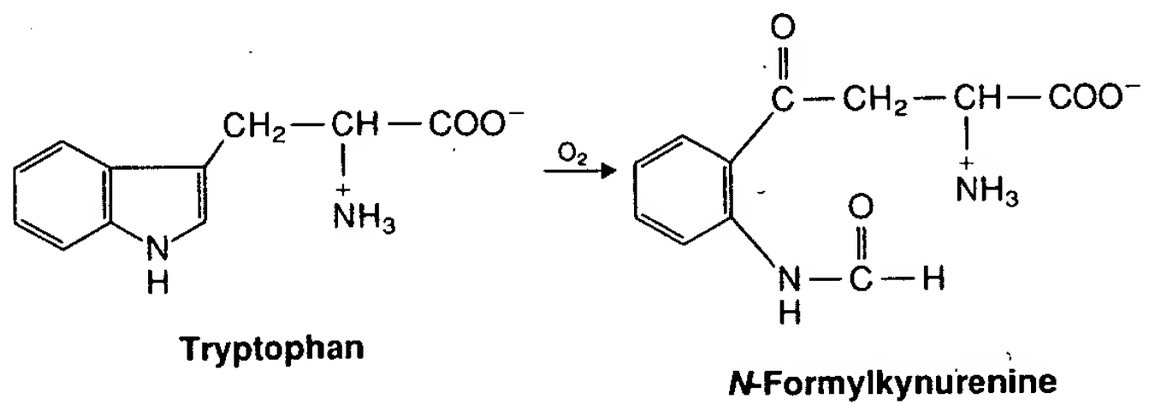
Oxidases and Oxygenases

The term **oxidase** is applied to enzymes that catalyze the oxidation of a substrate by O_2 without incorporation of oxygen into the product. Since a two-electron oxidation is usually involved, the oxygen is converted to H_2O_2. Most oxidases utilize either a metal or a flavin coenzyme. D-Amino acid oxidases, for example, use FAD as a cofactor.



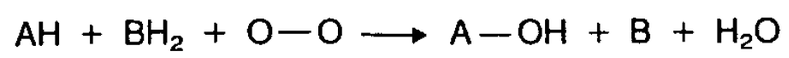
$$\mathrm{FADH_2 + O_2 \longrightarrow FAD + H_2O_2}$$

Oxygenases are enzymes that incorporate oxygen from O_2 into the oxidized products. **Dioxygenases,** which incorporate both atoms of O_2 into one substrate, are of limited distribution. An example is tryptophan 2,3-dioxygenase which catalyzes the first reaction in tryptophan catabolism (below). This enzyme contains a heme cofactor.



Tryptophan **N-Formylkynurenine**

Far more widely distributed are **monooxygenases,** which incorporate one atom from O_2 into a product, the other atom being reduced to water. A monooxygenase has one substrate that accepts oxygen and another that furnishes two H atoms that reduce the other oxygen to water. Because two substrates are oxidized, this class of enzymes is also called **mixed-function oxidases.** The general reaction catalyzed by these enzymes is as follows.



Since the substrate AH usually becomes hydroxylated by this class of enzymes, the term **hydroxylase** is also used. An example of this type of reac-

1: J Food Prot. 2000 Jun;63(6):747-52.

Antibacterial activity of a chitooligosaccharide mixture prepared by cellulase digestion of shrimp chitosan and its application to milk preservation.

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The antibacterial activity of a chitooligosaccharide mixture prepared by digestion of shrimp chitosan with cellulase at 50 degrees C for 14 h was evaluated. Sugars with 1 to 8 degrees of polymer (DP) were found in this chitooligosaccharide mixture, and the weight percentage of sugars with DP > or = 6 was 44.3%. Minimal lethal concentrations of this mixture against Aeromonas hydrophila, Escherichia coli, Listeria monocytogenes, Pseudomonas aeruginosa, Salmonella Typhimurium, Shigella dysenteriae, Staphylococcus aureus, Vibrio cholerae, and Vibrio parahaemolyticus in nutrient broth were 5 to 29 ppm, which were much lower than those of the chitosan reactant (50 to 1,000 ppm). The antibacterial activity of this mixture in the sterilized milk against E. coli O157, L. monocytogenes, Salmonella Typhimurium, and S. aureus was much stronger at 4 degrees C than at 37 degrees C. When raw milk was supplemented with either 0.24% or 0.48% (wt/vol) of this oligosaccharide mixture and stored at 4 degrees C for 12 days, its mesophilic and psychrotrophic counts were reduced by at least 3 log cycles, and there was very little change in pH. In addition, this mixture retarded the growth of Salmonella species and caused quicker reduction of Staphylococcus species in raw milk. Accordingly, the shelf life of raw milk at 4 degrees C was extended by at least 4 days.

PMID: 10852568 [PubMed - indexed for MEDLINE]

1: J Food Prot. 2004 Feb;67(2):396-8.

Antimicrobial activity of a low-molecular-weight chitosan obtained from cellulase digestion of chitosan.

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A water-soluble chitosan hydrolysate with high activity against Escherichia coli was obtained during cellulase digestion of chitosan for 18 h. This 18-h hydrolysate is composed of low-molecular-weight chitosan (LMWC), with a molecular weight of 12.0 kDa, and chitooligosaccharides, which are composed of sugars with a degree of polymerization of 1 to 8. LMWC has a strong activity at 100 ppm against many pathogens and yeast species, including Bacillus cereus, E. coli, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella enterica serovar Typhi, and Saccharomyces cerevisiae, while the chitooligosaccharides have much weaker antimicrobial activity than does LMWC. Accordingly, the antimicrobial activity against E. coli in the 18-h hydrolysate proved to come mainly from the presence of LMWC.

PMID: 14968977 [PubMed - indexed for MEDLINE]

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